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(57) Abstract

The invention provides a complexant compound of formula (I): $R^3S(CR^1_2)_nN(R^2)_i(CR^1_2)_nX(CR^1_2)_nN(R^2)_i(CR^1_2)_nSR^3$, (wherein each n, which may be the same or different, is an integer 2, 3 or 4 (preferably 2); each i, which may be the same or different, represents 0 or 1; each R^3, which may be the same or different, is H or a thiol protecting group, preferably a protecting group; X is O, S, N, NR^4 or a substituted phosphorus (e.g. oxo substituted phosphorus), preferably S or N; each R^4, which may be the same or different, is hydrogen or an optionally substituted organic group; each R^2, which may be the same or different, is hydrogen or an optionally substituted organic group; each R^1, which may be the same or different, is hydrogen or an optionally substituted organic group, or a moiety CR^1_2 may represent a carbonyl group or two, three or four R^1S on two different carbons together with those carbons and any intervening atoms may represent an optionally substituted saturated or unsaturated homocyclic or heterocyclic ring; and preferably, at least one CR^1_2 moiety is other than CH_2 or $CH(CH_3)$) or a salt or complex thereof, wherein optionally at least one of the R^1, R^2, R^3 and R^4 moieties is coupled directly or indirectly to a vector moiety.

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CHELATING AGENTS

This invention relates to complexants and metallated complexes thereof and to their use in diagnostic, therapeutic and prophylactic compositions, in particular to the use of such complexants metallated with radionuclides as diagnostic imaging and therapeutic agents.

Radiopharmaceuticals, the class of drug compounds containing radionuclides, are useful for the diagnosis and treatment of various disease states, in particular certain cancers.

The radionuclide in such radiopharmaceuticals may be a metal (eg. a transition metal or lanthanide) or a non-metal (eg. an iodine or hydrogen radionuclide). Where the radionuclide is a metal, it is conventionally administered as a complex (usually a chelate complex) of a mono- or polyatomic ion of or containing the metal, with a complexing agent. The present invention is particularly concerned with complexed metal radionuclides and complexants which can be metallated with metal ion radionuclides.

In the use of complexed metal radiopharmaceuticals, the diagnostic or therapeutic properties are selected by appropriate selection of the metal radionuclide (eg. by virtue of its decay pattern or half life) while the biodistribution and bioelimination properties are selected by appropriate selection of the complexant and, if desired of a vector moiety coupled directly or indirectly to the complexant so as to cause the complexed radionuclide to be targeted to a particular body site or tissue type, eg. cancerous tissue.

Examples of complexants that have been proposed for use with metal radionuclides in therapeutic or diagnostic compositions include the terpyridine chelants disclosed in WO-A-92/08494 and WO-A-93/21957 and the BAT chelants discussed by Ohmomo et al. in J. Med. Chem. 35: 157-162 (1992) and by Kung et al. in J. Nucl. Med. 25: 326-332 (1984).

Nevertheless there is a continuing need for complexants which are capable of adequately complexing diagnostic and therapeutic metal radionuclides and which preferably also may be coupled to effective vector moieties so as to target the complexed radionuclide to a desired target site within the patient's body.

In particular there is a continuing need for complexants that may be used to complex both diagnostically effective metal radionuclides and therapeutically effective metal radionuclides. In this way a disease site may be imaged and treated using diagnostic and therapeutic agents which have substantially identical biodistributions since the carrier portion of the metal: carrier complex, which determines the biodistribution pattern of the complex, may be the same in both the diagnostic agent and the therapeutic agent.

We have now found that a new class of complexants possesses appropriate properties in this regard.

The novel complexants are referred to as N_2S_2X complexants since they contain a carbon chain interrupted, in order by S, N, X, N and S heteroatoms (where X is an O, S, N or P heteroatom). Between these heteroatoms there are carbon chains 2, 3 or 4 atoms long. Such complexants, and the salts and complexes thereof, including the targeted complexes thereof, form one aspect of the invention.

Viewed from a further aspect the invention provides a complexant compound of formula I

$$R^3S(CR^1_2)_nN(R^2)_i(CR^1_2)_nX(CR^1_2)_nN(R^2)_i(CR^1_2)_nSR^3 \quad (I)$$

(wherein each n, which may be the same or different, is an integer 2, 3 or 4 (preferably 2);
each i, which may be the same or different, represents 0 or 1;
each R^3, which may be the same or different, is H or a thiol protecting group, preferably a protecting group;
X is O, S, N, NR^4 or a substituted phosphorus (eg. oxo substituted phosphorus), preferably S or N;
each R^4, which may be the same or different, is hydrogen or an optionally substituted organic group;
each R^2, which may be the same or different, is hydrogen or an optionally substituted organic group;
each R^1, which may be the same or different, is hydrogen or an optionally substituted organic group, or a moiety CR^1_2 may represent a carbonyl group or two, three or four R^1s on two different carbons together with those carbons and any intervening atoms may represent an optionally substituted saturated or unsaturated homocyclic or heterocyclic ring; and preferably, at least one CR^1_2 moiety is other than CH_2 or $CH(CH_3)$) or a salt or complex thereof, wherein optionally at least one of the R^1, R^2, R^3 and R^4 moieties is coupled directly or indirectly to a vector moiety.

Viewed from a further aspect the invention provides a pharmaceutical composition comprising an effective amount (eg. an amount effective to enhance image contrast in in vivo imaging or an amount sufficient to achieve a desired therapeutic effect) of a complex of an optionally vector coupled complexant of formula I together with at least one pharmaceutically effective carrier or excipient.

Viewed from a still further aspect the invention provides the use of a complex of an optionally vector coupled complexant of formula I for the manufacture of a contrast medium for use in a method of diagnosis involving administration of said contrast medium to an animate subject and generation of an image of at least part of said subject.

Viewed from a still further aspect the invention provides the use of a complex of an optionally vector coupled complexant of formula I for the manufacture of a therapeutic agent, eg. a radiopharmaceutical, for example for use in tumor therapy.

Viewed from a still further aspect the invention provides a method of generating an image of an animate human or non-human (preferably mammalian or avian) animal subject involving administering a contrast agent to said subject, eg. into the vascular system or the gi tract, and generating an image of at least a part of said subject to which said contrast agent has distributed, eg. by X-ray, MR, ultrasound, scintigraphic, PET, SPECT, electrical impedance, light or magnetometric imaging modalities, characterised in that as said contrast agent is used a complex of an optionally vector coupled complexant of formula I.

Viewed from a still further aspect the invention provides a method of treatment of an animate human or non-human (preferably mammalian or avian) animal subject involving administering a therapeutic agent to said subject, eg. into the vascular system or the gi tract, characterised in that as said therapeutic agent is used a complex of an optionally vector coupled complexant of formula I.

Viewed from a yet further aspect the invention provides

a process for the preparation of a complex of an optionally vector coupled complexant of formula I, said process comprising metallating an optionally vector coupled complexant of formula I with a diagnostically or therapeutically effective metal ion or metal-containing complex ion.

Metallation may be effected using conventional techniques, eg. reacting the complexant or a salt thereof in solution with a soluble salt of the desired metal.

Where, in the compounds of formula I, R^1 groups together with intervening atoms form a cyclic group it is particularly preferred that this be a 5 to 8 membered ring containing 0, 1, 2 or 3 heteroatoms selected from N, S and O. More especially it is preferred that one such heteroatom is provided by a $N(R^2)_i$ or X group and it is even more especially preferred that the R^1 groups are on two carbons adjacent but on different sides of an $N(R^2)_i$ or X group. Preferably the compound of formula I will contain zero, one or three such heterocycles, preferably unsaturated and especially preferably aromatic heterocycles, incorporating ring nitrogens oxygens or sulphurs from $N(R^2)_i$ and X moieties. Particularly preferably the resultant heterocycle is an unsaturated N_1, N_2, O_1, N_1O_1 or S_1 heterocycle, preferably a thiophene, pyrrolidine, piperidine, piperazine, morpholine, pyran, pyrrole, imidazole, pyrazine, pyrimidine, imidazolidine, imidazolidinone, furan or pyridine ring. Pyridine, thiophen and furan rings, especially pyridine rings are especially preferred.

It is also preferred that the two $(CR^1_2)_n$ groups between the $N(R^2)_i$ and X moieties should be $(CH_2)_n$ or $(CR^1_2)(CH_2)_{n-1}$ groups where X is S and where the CR^1_2 moieties are attached to the $N(R^2)_i$ nitrogens. It is further

preferred that the (CR^1_2) groups adjacent a (CR^1_2) group which is part of a cyclic group themselves should be part of a cyclic group or should be CH or CH_2 groups.

It is moreover preferred that the CR^1_2 moieties adjacent SR^3 groups should be CH_2 or CR^5_2 groups (where each R^5 is independently an alkyl group, preferably a C_{1-3} alkyl group), especially preferably CH_2 or $C(CH_3)_2$ groups. Such CR^1_2 moieties are preferably CR^5_2 groups where the adjacent $(CR^1_2)_{n-1}N(R^2)_i$ group does not form part of a cyclic group.

Where a CR^1_2 group is a carbonyl group, this is preferably adjacent a $N(R^2)_i$ group. Where such a carbonyl group is present it is preferred that the other CR^1_2 group adjacent the $N(R^2)_i$ group should contain an amine or carbonyl function, eg. such a CR^1_2 group is a group $CH\text{-}CH_2COOH$ or $CH\text{-}CH_2CH_2NH_2$.

Any cyclic group formed by two CR^1_2 groups and intervening atoms may, as indicated above, be optionally substituted, eg. by at least one hydroxy, oxo, halo, alkyl, aryl, amino, CNS, carboxyl or acyl group, eg. by a hydroxy-amino-phenyl group.

Organic groups which are substituents on the compound of formula I will generally be C_{1-20} groups, preferably C_{1-10} groups, optionally containing one or more, eg. up to six heteroatoms (eg. halo, N, S, P and O atoms). Alkyl, alkenyl, alkynyl and acyl moieties (including alkylene etc. moieties) will preferably contain up to 6 carbon atoms. Aryl moieties will preferably be phenyl groups or 5 to 7 membered N, S or O heterocycles. However other hydrophilic substituents, such as polyalkylene oxides (ie. $((CH_2)_mO)_p$ where m is 2 or 3 and p is an integer of 2 to 500) may be present if desired as biodistribution modifiers.

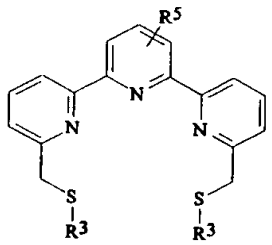
Where two NR^2_i groups are present, it is preferred that in at least one R^2 is an amine, carboxyl, or sulfur or phosphorus oxy-acid substituted C_{1-6} alkyl group, eg. $CH_2CH_2NH_2$ or, more preferably, CH_2COOH.

Preferably the compounds of formula I are of formula II

$$R^3\text{-}S\text{-}CR^4_2(CH_2)_{n-2}(CR^1_2)N(R^2)_i(CR^1_2)(CH_2)_{n-2}(CR^1_2)X(CR^1_2)\text{-}(CH_2)_{n-2}(CR^1_2)N(R^2)_i(CR^1_2)(CH_2)_{n-2}CR^4_2SR^3 \qquad (II)$$

where each CR^1_2, which may be the same or different, is CH_2, CH or C, in the later cases being linked to a CR^1_2 group adjacent the same heteroatom to form an optionally substituted saturated or unsaturated 5 or 6-membered heterocycle, and each R^2 where present is H or a functionalized C_{1-6} alkyl group (eg. CH_2COOH), preferably one R^2 being other than H.

Particularly preferably, each n is 2, x is S or N and 0, 1 or 2 fused pyridine groups are present in the compounds of the invention. Thus, particularly preferred compounds include those of formulae III to VII:



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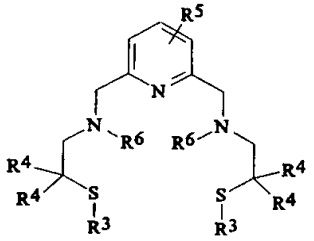

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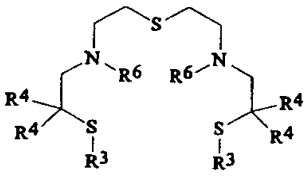

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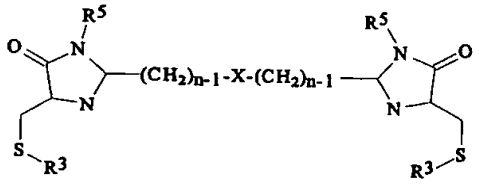

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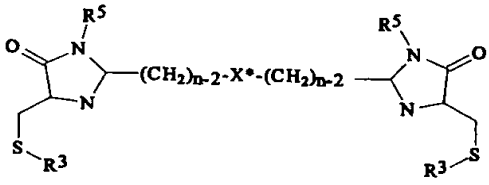


(VII)

(where R^5 is hydrogen or optionally substituted alkyl, aryl, alkaryl or aralkyl;
R^4 is H or, preferably, CH_3;
R^6 is H or functionalized alkyl, preferably one being H and the other being CH_2COOH; and X* is a carbon attached heteroaromatic ring, eg. a 2,5-thiophene, 2,6-pyridine,

2,5-furan or 2,6-pyrimidine ring, optionally substituted by a R^5 group).

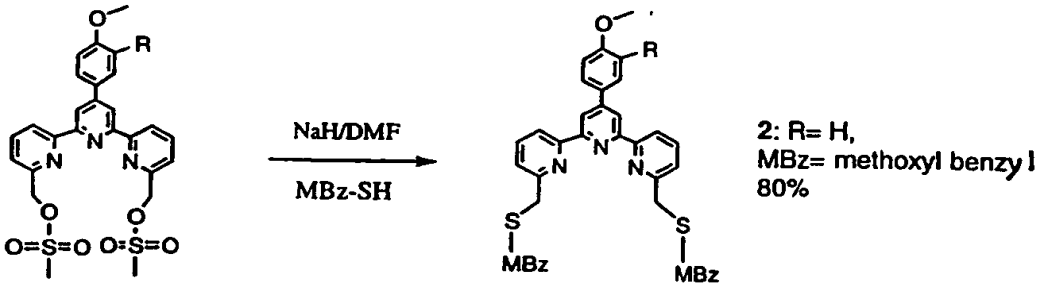
Direct linkage to a vector group is preferably via a backbone carbon of a $(CR^1_2)_n$ moiety or via a ring carbon of a cyclic group formed by two (CR^1_2) groups and an intervening heteroatom of $N(R^2)_i$ or X, particularly preferably via a phenyl group attached to such a ring atom.

The thiol protecting group R^3 may be any of the known thiol protecting groups (see for example Greene, "Protective groups in organic synthesis", Wiley Interscience, 1981 and McOmie, "Protective groups in organic chemistry", Plenum, 1973). Examples of such groups include optionally substituted C_{1-6} alkyl groups, eg. methoxy benzyl (mBz) groups.

The complexants of the invention may be coupled to a vector, a material which will affect the biodistribution of the complexant or its complexes, eg. to target it to particular receptors, organs, tissues or body compartments. Such coupling may be direct or may involve a linker, a bifunctional compound which binds to the complexant and the vector. Examples of suitable vectors include proteins, antibodies, antibody fragments, oligopeptides, hormones, polyalkylene oxides, and pharmaceuticals. (See for example WO 92/08494).

The compounds of the invention may be prepared by routine organic synthesis and chelator metallation techniques. Illustrative synthetic schemes are shown below.

Scheme 1. Synthesis of TMT-S2



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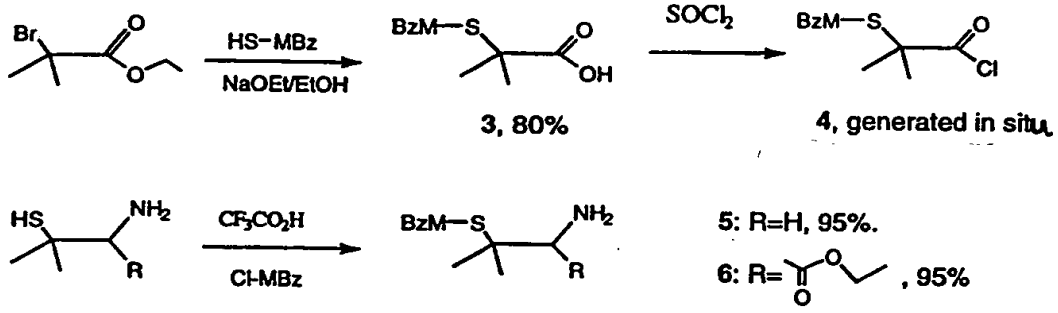
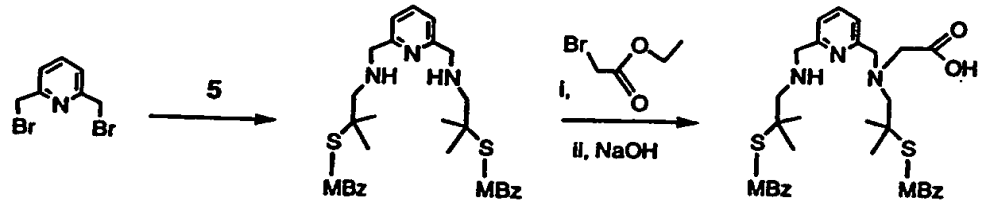
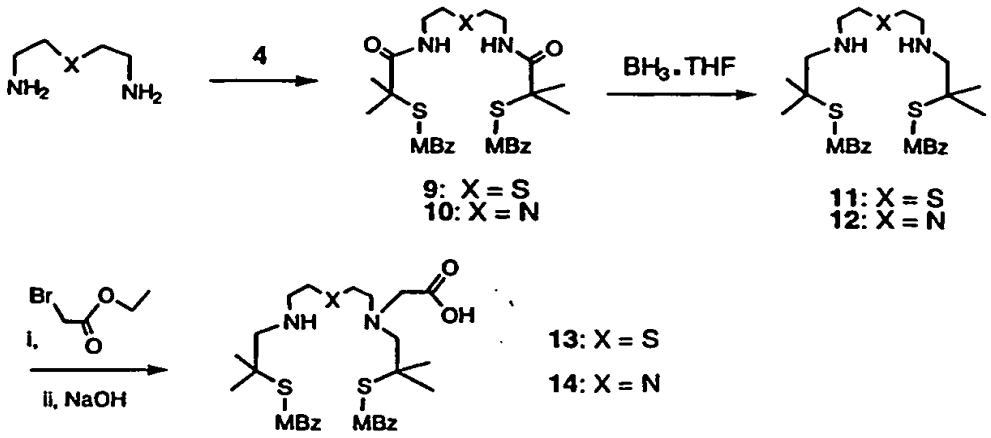
Scheme 2. Synthesis of precursors



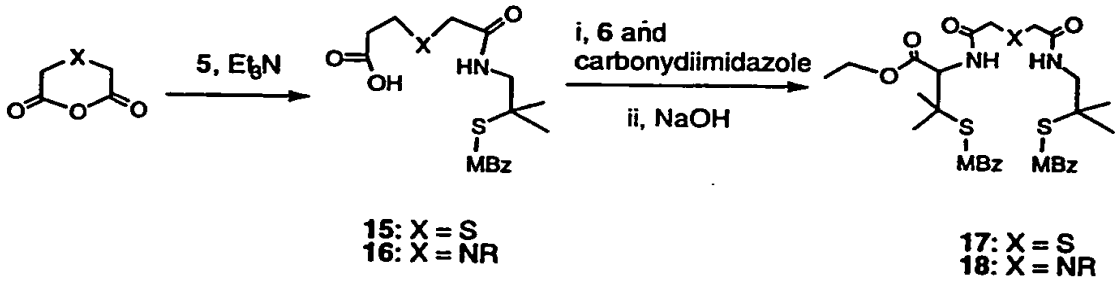
Scheme 3. Synthesis of N2S2-pyridine



Scheme 4. Synthesis of N2S2X



5. Synthesis of N2S2X-amide



The complexant compounds of formula I may be metallated with therapeutically or diagnostically effective metal ions or complex ions (eg. metal oxide or metal sulphide ions (such as TcO or VO)). Generally speaking, preferred metal ions will be radionuclides, paramagnetic ions, fluorescent ions, or heavy metal ions (eg. with atomic number greater than 53) or cluster ions.

Examples of apprpriate metals include Ag, At, Au, Bi, Cu, Ga, Ho, In, Lu, Pb, Pd, Pm, Pr, Rb, Re, Rh, Sc, Sr, Tc, Tl, Y, and Yb.

Preferred metal radionuclides include ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au,

^{203}Pb and ^{141}Ce.

Moreover γ-emitting radionuclides, such as ^{99m}Tc, ^{111}In, ^{67}Ga and ^{169}Yb have been approved or under investigation for diagnostic imaging, while complexes of β-emitters, such as ^{67}Cu, ^{111}Ag, ^{186}Re and ^{90}Y are most promising for the applications in tumor therapy. Also γ-emitters (examples are ^{99m}Tc, ^{111}In, ^{67}Ga and ^{169}Yb) but also to the β-emitters (such as ^{67}Cu, ^{111}Ag, ^{186}Re, ^{188}Re and ^{90}Y), as well as other radionuclides of interest (^{211}At, ^{212}Bi, ^{177}Lu, ^{86}Rb, ^{105}Rh, ^{153}Sm, ^{198}Au, ^{149}Pm, ^{85}Sr, ^{142}Pr, ^{214}Pb, ^{109}Pd, ^{166}Ho, ^{208}Tl, and ^{44}Sc). Complexes with hard metal ions, such as In^{3+}, Ga^{3+}, Yb^{3+}, and Y^{3+}, shall be stable. In addition, since they contain two or three sulfur atoms, their soft metal (Ag^{+}, Cu^{2+}, TcO^{3+}, and ReO^{3+}) complexes should also be stable.

Preferred paramagnetic metal ions include ions of transition and lanthanide metals (eg. metals having atomic numbers of 6 to 9, 21-29, 42, 43, 44, or 57-71), in particular ions of Cr, V, Mn, Fe, Co, Ni, Cu, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu, especially of Mn, Cr, Fe, Gd and Dy, more especially Gd.

Preferred fluorescent metal ions include lanthanides, in particular La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu. Eu is especially preferred.

Preferred heavy metal-containing reporters may include atoms of Mo, Bi, Si, and W, and in particular may be polyatomic cluster ions (eg. Bi compounds and W and Mo oxides) as described in WO91/14460, WO92/17215, WO96/40287, and WO96/22914.

All of the publications referred to herein are incorporated herein by reference.

The compounds of the invention may be administered to patients for imaging in amounts sufficient to yield the desired contrast with the particular imaging technique. Generally dosages of from 0.001 to 5.0 mmoles of chelated imaging metal ion per kilogram of patient bodyweight are effective to achieve adequate contrast enhancements. For most MRI applications preferred dosages of imaging metal ion will be in the range of from 0.02 to 1.2 mmoles/kg bodyweight while for X-ray applications dosages of from 0.05 to 2.0 mmoles/kg are generally effective to achieve X-ray attenuation. Preferred dosages for most X-ray applications are from 0.1 to 1.2 mmoles of the lanthanide or heavy metal compound/kg bodyweight. Where the chelated species is a radionuclide, dosages of 0.01 to 100 mCi, preferably 0.1 to 50 mCi will normally be sufficient per 70 kg bodyweight.

The dosage of the compounds of the invention for therapeutic use will depend upon the condition being treated, but in general will be of the order of from 1 pmol/kg to 1 mmol/kg bodyweight.

The compounds of the present invention may be formulated with conventional pharmaceutical or veterinary aids, for example emulsifiers, fatty acid esters, gelling agents, stabilizers, antioxidants, osmolality adjusting agents, buffers, pH adjusting agents, etc., and may be in a form suitable for parenteral or enteral administration, for example injection or infusion or administration directly into a body cavity having an external escape duct, for example the gastrointestinal tract, the bladder or the uterus. Thus the compounds of the present invention may be in conventional pharmaceutical administration forms such as tablets, capsules, powders, solutions, suspensions, dispersions, syrups, suppositories etc. However, solutions, suspensions and dispersions in

physiologically acceptable carrier media, for example water for injections, will generally be preferred.

The compounds according to the invention may therefore be formulated for administration using physiologically acceptable carriers or excipients in a manner fully within the skill of the art. For example, the compounds, optionally with the addition of pharmaceutically acceptable excipients, may be suspended or dissolved in an aqueous medium, with the resulting solution or suspension then being sterilized.

For imaging of some portions of the body the most preferred mode for administering contrast agents is parenteral, e.g., intravenous administration. Parenterally administrable forms, e.g. intravenous solutions, should be sterile and free from physiologically unacceptable agents, and should have low osmolality to minimize irritation or other adverse effects upon administration, and thus the contrast medium should preferably be isotonic or slightly hypertonic. Suitable vehicles include aqueous vehicles customarily used for administering parenteral solutions such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection and other solutions such as are described in Remington's Pharmaceutical Sciences, 15th ed., Easton: Mack Publishing Co., pp. 1405-1412 and 1461-1487 (1975) and The National Formulary XIV, 14th ed. Washington: American Pharmaceutical Association (1975). The solutions can contain preservatives, antimicrobial agents, buffers and antioxidants conventionally used for parenteral solutions, excipients and other additives which are compatible with the chelates and which will not interfere with the manufacture, storage or use of products.

The invention is illustrated further by the following non-limiting Examples. Compound numbering is as in the reaction schemes illustrated above.

Example 1

Preparation of 2: To a solution of 76 mg of NaH in 10 mL DMF under N_2, 0.27 mL of 4-methoxyl benzyl thiol was added while stirring. Then 0.48 g WIN 63539 solid was added, the mixture was stirred overnight. The mixture was diluted with $CHCl_3$, washed with H_2O, 10% Na_2CO_3 and brine, dried over Na_2SO_4. It was filtered and **2** was obtained as an off-white solid after the solvent was removed by rotary evaporation. The yield is 80% and 2 was characterized by TLC and NMR.

Example 2

Preparation of 3 and 4: 3 was prepared through a known procedure by reaction of ethyl 2-bromo-2-methyl propionate with HS-MBz in sodium ethoxide/ethanol with yields between 60% to 80%. The crude product was used in the subsequent *in situ* generation of **4**.

Example 3

Preparation of 5: To a solution of 18.2 g of 1-Amino-2-methyl-2-propanethiol hydrochloride in 150 mL CH_2Cl_2 and 21 mL trifloroacetic acid at 0°C, a cold solution of 20.1 g 4-methoxylbenzyl chloride in 50 mL CH_2Cl_2 was added dropwise. The mixture was stirred at 0°C for 1 hr and in room temperature for 3 hr. MeOH 30 mL was added to the mixture to terminate the reaction and all solvents was removed by rotary evaporation. The residue was dissolved in 400 mL $CHCl_3$, washed with sat. $NaHCO_3$ 3x300 mL, 10% Na_2CO_3, H_2O, and brine, dried over Na_2SO_4. It was filtered and 5 was obtained as a colorless oil

after the solvent was removed by rotary evaporation. The yield was 95% and **5** was characterized by TLC and NMR.

Example 4

Preparation of **6**: It was prepared by same procedure as that of **5** using L-Cysteine ethyl ester hydrochloride. The yield was 95% and **6** was characterized by TLC and NMR.

Example 5

Preparation of **7**: To a solution of 2,6-bis(bromomethyl)pyridine in MeCN, diisopropyl ethylamine and **5** were added. The mixture was heated to reflux for 3 days and allowed to cool to room temperature. Extraction techniques and silica chromatography afforded **7**.

Example 6

Preparation of **8**: To a solution of **7** in MeCN, diisopropyl ethylamine and ethyl bromoacetate are added, the mixture is heated to reflux overnight and usual extraction techniques and silica chromatography afford **8**.

Example 7

Preparation of **9**: To a solution of **3** (5 g) in $CHCl_3$, 6.6 mL $SOCl_2$ was added dropwise, then the mixture was refluxed for 3 hr. Solvent was removed by rotary evaporation and 50mL CH_2Cl_2 was added to the residue at 0°C. 3.4 mL Et_3N was added slowly and then a solution of 1.1 g 2,2'-bisaminoethyl thioether in 10 mL CH_2Cl_2 was added dropwise. The mixture was allowed to warm to room temperature and then was heated to reflux for 3 hr. It

was allowed to cool to room temperature and was transferred to a separation funnel, washed with sat. $NaHCO_3$, 10% Na_2CO_3, H_2O, 1N HCl, H_2O, and brine, dried over Na_2SO_4. It was filtered and the crude product was obtained after the solvent was removed by rotary evaporation. It was purified by silica chromatography (50% : 50%/ethyl acetate : hexane) and **9** was obtained as a colorless oil. The yield was 50% and **9** was characterized by TLC and NMR.

Example 8

Preparation of **10**: It is prepared and isolated in a similar procedure as to that of **9**, using diethylene triamine. Usual isolation and purification procedures afford a pure product.

Example 9

Preparation of **11**: To a solution of 5.3 g **9** in 40 mL of THF, 40 mL of 1 N BH_3•THF was added. The mixture was heated to reflux for 48 hr and was allowed to cool to room temperature. About 10 mL 6 N NaOH was added to decompose the excess BH_3 and the mixture was refluxed for 30 min. 2 N HCl was added to adjust pH to acidic, and all solvent was removed by rotary evaporation. The residue was dissolved in CHCl3, washed with H_2O, sat. $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4. It was filtered and the crude product was purified by silica chromatography (90% : 10%/ethyl acetate : MeOH) and **11** was obtained as a colorless oil. The yield was ~ 50% and **11** was characterized by TLC and NMR.

Example 10

Preparation of **12**: It is prepared and isolated in a similar procedure as to that of **11**, using **10** as the

starting material. Usual isolation and purification procedures afford a pure product.

Example 11

Preparation of **13**: To a solution of 2.9 g **11** in 100 mL MeCN, 0.79 g diisopropylethyl amine and 0.94 g ethyl bromoacetate were added. The mixture was heated to reflux for 24 hr and was allowed to cool to room temperature. Solvent was removed by rotary evaporation and the residue was dissolved in $CHCl_3$, washed with H_2O, sat. $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4. It was filtered and the crude product was purified by silica chromatography (90% : 10% / ethyl acetate : hexane). It was dissolved in a mixture of 20mL THF and 20 mL 5 N NaOH. The mixture was refluxed for 1 hr and was allowed to cool to room temperature. The pH of the solution was adjusted to ~10 with 1 N HCl and it was extracted with CH_2Cl_2. The organic phase was washed with H_2O, 10% Na_2CO_3, H_2O, and brine, dried over Na_2SO_4. It was filtered and **13** was obtained as a white solid. The final yield was ~ 40% and **13** was characterized by TLC and NMR.

Example 12

Preparation of **14**: It is prepared and isolated in a similar procedure as to that of **13**, using **12** as the starting material. Usual isolation and purification procedures afford a pure product.

Example 13

Preparation of **15**: To a solution of 8.6 g **5** in 150 mL CH_2Cl_2 at 0°C, 5.3 g thioglycolic anhydride solid was added slowly and the mixture was stirred for 4 hr. It was transferred to a separation funnel, washed with H_2O, 10% Na_2CO_3, H_2O, and brine, dried over Na_2SO_4. It was

filtered and **15** was obtained as a colorless oil after the solvent was removed by rotary evaporation. The yield was 90% and **15** was characterized by TLC and NMR.

Example 14

Preparation of **16**: It is prepared and isolated in a similar procedure as to that of **15**, using amine-protected iminodiacetic anhydride as the starting material. Usual isolation and purification procedures afford a pure product.

Example 15

Preparation of **17**: To a solution of 6.5 g **15** in 150 mL $CHCl_3$, 4.4 g carbonyldiimidazole solid was added slowly and the mixture was stirred for 30 min. Then a solution of 5.7 g **6** in 50 mL $CHCl_3$ was added and the mixture was stirred overnight. It was transferred to a separation funnel, washed with H_2O, 1N HCl, H_2O 10% Na_2CO_3, H_2O, and brine, dried over Na_2SO_4. It was filtered and the crude product was purified by silica chromatography (90% : 10% /ethyl acetate : hexane). The yield was 60% and **17** was characterized by TLC and NMR.

Example 16

Preparation of **18**: It is prepared and isolated in a similar procedure as to that of **17**, using **16** as the starting material. Usual isolation and purification procedures afford a pure product.

Claims

1. A complexant compound of formula I

$$R^3S(CR^1_2)_nN(R^2)_i(CR^1_2)_nX(CR^1_2)_nN(R^2)_i(CR^1_2)_nSR^3 \quad (I)$$

(wherein each n, which may be the same or different, is an integer 2, 3 or 4;
each i, which may be the same or different, represents 0 or 1;
each R^3, which may be the same or different, is H or a thiol protecting group;
X is O, S, N, NR^4 or a substituted phosphorus;
each R^4, which may be the same or different, is hydrogen or an optionally substituted organic group;
each R^2, which may be the same or different, is hydrogen or an optionally substituted organic group;
each R^1, which may be the same or different, is hydrogen or an optionally substituted organic group, or a moiety CR^1_2 may represent a carbonyl group or two, three or four R^1s on two different carbons together with those carbons and any intervening atoms may represent an optionally substituted saturated or unsaturated homocyclic or heterocyclic ring) or a salt or complex thereof, wherein optionally at least one of the R^1, R^2, R^3 and R^4 moieties is coupled directly or indirectly to a vector moiety.

2. A compound as claimed in claim 1 wherein at least one CR^1_2 moiety is other than CH_2 or $CH(CH_3)$, or a salt or complex thereof.

3. A compound as claimed in claim 1 or claim 2 wherein n is 2, each R^3 is independently a thiol protecting group, and X is S or N, or a salt or complex thereof.

4. A compound as claimed in any one of claims 1 to 3 comprising zero, one, two or three heterocyclic rings

incorporating ring nitrogens, oxygens or sulphurs from $N(R^2)_i$ and X moieties.

5. A compound as claimed in any one of claims 1 to 4 wherein the two $(CR^1_2)_n$ groups between the $N(R^2)_i$ and X moieties are $(CH_2)_n$ or $(CR^1_2)(CH_2)_{n-1}$ groups where X is S and where the CR^1_2 moieties are attached to the $N(R^2)_i$ nitrogens.

6. A compound as claimed in any one of claims 1 to 5 wherein the (CR^1_2) groups adjacent a (CR^1_2) group which is part of a cyclic group themselves form part of a cyclic group or are CH or CH_2 groups.

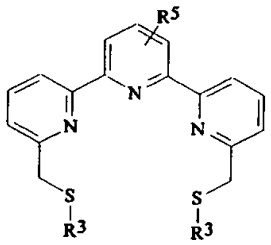
7. A compound as claimed in any preceding claim wherein the CR^1_2 moieties adjacent SR^3 groups are CH_2 or CR^5_2 groups in which each R^5 is independently an alkyl group.

8. A compound as claimed in claim 1 of formula II

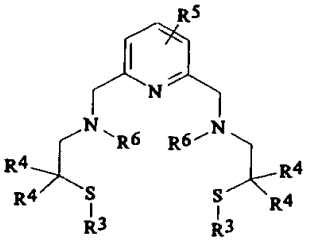
$$R^3\text{-}S\text{-}CR^4_2(CH_2)_{n-2}(CR^1_2)N(R^2)_i(CR^1_2)(CH_2)_{n-2}(CR^1_2)X(CR^1_2)\text{-}(CH_2)_{n-2}(CR^1_2)N(R^2)_i(CR^1_2)(CH_2)_{n-2}CR^4_2SR^3 \qquad (II)$$

(wherein each CR^1_2, which may be the same or different, is CH_2, CH or C, in the later cases being linked to a CR^1_2 group adjacent the same heteroatom to form an optionally substituted saturated or unsaturated 5 or 6-membered heterocycle, and each R^2 where present is H or a functionalized C_{1-6} alkyl group) or a salt or complex thereof.

9. A compound as claimed in claim 1 of formulae III to VII:



(III)



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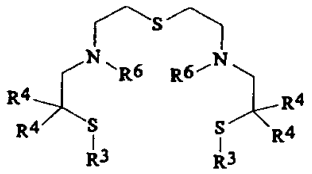
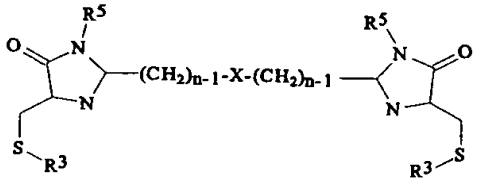
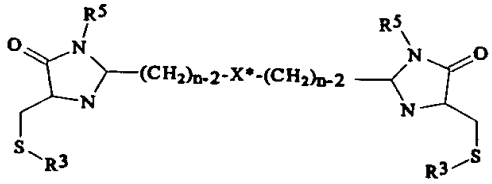


(V)



(VI)



(VII)

(where R^5 is hydrogen or optionally substituted alkyl, aryl, alkaryl or aralkyl;
R^4 is H or CH_3;
R^6 is H or functionalized alkyl; and
X* is a carbon attached heteroaromatic ring, optionally substituted by a R^5 group) or a salt or complex thereof.

10. A compound as claimed in any preceding claim metallated by at least one metal ion or complex ion.

11. A compound as claimed in claim 10 wherein said metal ion is selected from radionuclides, paramagnetic ions, fluorescent ions, heavy metal ions and cluster ions.

12. A compound as claimed in claim 10 wherein said metal ion is selected from metal ions of Ag, At, Au, Bi, Cu, Ga, Ho, In, Lu, Pb, Pd, Pm, Pr, Rb, Re, Rh, Sc, Sr, Tc, Tl, Y, and Yb.

13. A compound as claimed in claim 11 wherein said radionuclide is selected from ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{203}Pb and ^{141}Ce.

14. A compound as claimed in claim 11 wherein said paramagnetic metal ion is selected from ions of transition and lanthanide metals, preferably metals having atomic numbers of 6 to 9, 21-29, 42, 43, 44, or 57-71.

15. A compound as claimed in any preceding claim coupled directly or indirectly to a vector moiety capable of targeting particular receptors, organs, tissues or body compartments.

16. A compound as claimed in claim 15 wherein said vector moiety is selected from proteins, antibodies, antibody fragments, oligopeptides, hormones, polyalkylene oxides, and pharmaceuticals.

17. A pharmaceutical composition comprising an effective amount of a compound as defined in any one of claims 1 to 16, or a salt or complex thereof, together

with at least one pharmaceutically effective carrier or excipient.

18. The use of a compound as defined in any one of claims 1 to 16, or a salt or complex thereof, for the manufacture of a contrast medium for use in a method of diagnosis involving administration of said contrast medium to an animate subject and generation of an image of at least part of said subject.

19. The use of a compound as defined in any one of claims 1 to 16, or a salt or complex thereof, for the manufacture of a therapeutic agent, preferably a radiopharmaceutical.

20. Use as claimed in claim 19 in the manufacture of a therapeutic agent for use in tumor therapy.

21. A method of generating an image of an animate human or non-human animal subject involving administering a contrast agent to said subject and generating an image of at least a part of said subject to which said contrast agent has distributed, preferably by X-ray, MR, ultrasound, scintigraphic, PET, SPECT, electrical impedance, light or magnetometric imaging modalities, characterised in that as said contrast agent is used a compound as defined in any one of claims 1 to 16, or a salt or complex thereof.

22. A method of treatment of an animate human or non-human animal subject involving administering a therapeutic agent to said subject, characterised in that as said therapeutic agent is used a compound as defined in any one of claims 1 to 16, or a salt or complex thereof.

23. A process for the preparation of a complex of an optionally vector coupled complexant of formula I as defined in claim 1, said process comprising metallating an optionally vector coupled complexant of formula I with a diagnostically or therapeutically effective metal ion or metal-containing complex ion.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K51/04 A61K49/04 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MIKAKO FUJITA ET AL.: "Metal-Chelating Inhibitors of a Zinc Finger Protein HIV-EP1. Remarkable Potentiation of Inhibitory Activity by Introduction of SH Groups." J. MED. CHEM., vol. 39, 1996, pages 503-507, XP002074962 * Page 503-504; see compounds: 2-6,17,18 * ---	1-4,6,7, 9-11,17, 19,22,23
X	MASAMI OTSUKA ET AL.: "Synthetic Inhibitors of Regulatory Proteins Involved in the Signaling Pathway of the Replication of Human Immunodeficiency Virus 1" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 5, no. 1, January 1997, pages 205-215, XP002074963 * See compounds 5-13 * ---	1-4,6,7, 9-11,17, 19,22,23

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[X] Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHIOTTELLIS E. ET AL.: "Comparative evaluation of Tc-Labeled Aminothiols as possible Brain Perfusion Imaging Agents" NUCL. MED. BIOL., vol. 15, no. 2, 1988, pages 215-223, XP002074964 * See Page 216, compounds 11-14 * see the whole document	1,2,4,7, 10-13, 17-19, 21-23
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/01078

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(74) Agents: GOLDING, Louise et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

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(57) Abstract

The invention provides a complexant compound of formula (I): $R^3S(CR^1_2)_nN(R^2)_i(CR^1_2)_nX(CR^1_2)_nN(R^2)_i(CR^1_2)_nSR^3$, (wherein each n, which may be the same or different, is an integer 2, 3 or 4 (preferably 2); each i, which may be the same or different, represents 0 or 1; each R^3, which may be the same or different, is H or a thiol protecting group, preferably a protecting group; X is O, S, N, NR^4 or a substituted phosphorus (e.g. oxo substituted phosphorus), preferably S or N; each R^4, which may be the same or different, is hydrogen or an optionally substituted organic group; each R^2, which may be the same or different, is hydrogen or an optionally substituted organic group; each R^1, which may be the same or different, is hydrogen or an optionally substituted organic group, or a moiety CR^1_2 may represent a carbonyl group or two, three or four R^1S on two different carbons together with those carbons and any intervening atoms may represent an optionally substituted saturated or unsaturated homocyclic or heterocyclic ring; and preferably, at least one CR^1_2 moiety is other than CH_2 or $CH(CH_3)$) or a salt or complex thereof, wherein optionally at least one of the R^1, R^2, R^3 and R^4 moieties is coupled directly or indirectly to a vector moiety.

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(57) Abstract

The invention provides a complexant compound of formula (I): $R^3S(CR^1_2)_nN(R^2)_i(CR^1_2)_nX(CR^1_2)_nN(R^2)_i(CR^1_2)_nSR^3$, (wherein each n, which may be the same or different, is an integer 2, 3 or 4 (preferably 2); each i, which may be the same or different, represents 0 or 1; each R^3, which may be the same or different, is H or a thiol protecting group, preferably a protecting group; X is O, S, N, NR^4 or a substituted phosphorus (e.g. oxo substituted phosphorus), preferably S or N; each R^4, which may be the same or different, is hydrogen or an optionally substituted organic group; each R^2, which may be the same or different, is hydrogen or an optionally substituted organic group; each R^1, which may be the same or different, is hydrogen or an optionally substituted organic group, or a moiety CR^1_2 may represent a carbonyl group or two, three or four R^1S on two different carbons together with those carbons and any intervening atoms may represent an optionally substituted saturated or unsaturated homocyclic or heterocyclic ring; and preferably, at least one CR^1_2 moiety is other than CH_2 or $CH(CH_3)$) or a salt or complex thereof, wherein optionally at least one of the R^1, R^2, R^3 and R^4 moieties is coupled directly or indirectly to a vector moiety.

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INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB 98/01078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K51/04 A61K49/04 A61K49/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MIKAKO FUJITA ET AL.: "Metal-Chelating Inhibitors of a Zinc Finger Protein HIV-EP1. Remarkable Potentiation of Inhibitory Activity by Introduction of SH Groups." J. MED. CHEM., vol. 39, 1996, pages 503-507, XP002074962 * Page 503-504; see compounds: 2-6,17,18 * ---	1-4,6,7, 9-11,17, 19,22,23
X	MASAMI OTSUKA ET AL.: "Synthetic Inhibitors of Regulatory Proteins Involved in the Signaling Pathway of the Replication of Human Immunodeficiency Virus 1" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 5, no. 1, January 1997, pages 205-215, XP002074963 * See compounds 5-13 * ---	1-4,6,7, 9-11,17, 19,22,23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
31 August 1998	10/09/1998

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/01078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	CHIOTTELLIS E. ET AL.: "Comparative evaluation of Tc-Labeled Aminothiols as possible Brain Perfusion Imaging Agents" NUCL. MED. BIOL., vol. 15, no. 2, 1988, pages 215-223, XP002074964 * See Page 216, compounds 11-14 * see the whole document	1,2,4,7, 10-13, 17-19, 21-23
X	WO 96 11918 A (MERCK FROSST CANADA INC ;FLANAGAN RICHARD J (CA); DUFOUR JEAN MARC) 25 April 1996 see page 3, line 15 - page 4, line 34; claims 1-12	1-4,7, 10-23
X	WO 94 04485 A (MALLINCKRODT MEDICAL INC) 3 March 1994 * see compound 24 * see claim 15	1,2,7, 10-12, 14,17, 18,21,23
A	WO 93 21957 A (STERLING WINTHROP INC) 11 November 1993 cited in the application see claims 1-18	1-23
A	WO 95 15769 A (IMMUNOMEDICS INC) 15 June 1995 see claim 8	15,16

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/ 01078

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 21-22 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-23
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/01078

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